REMARKS

Claims 76-81 and 101-119 are pending in the application. Claims 101-119 were added by the previous amendment filed May 24, 2007. The Examiner deemed new claims 109-119 patentably distinct and withdrew them from consideration.

Claims 76-81 were provisionally rejected on the ground obviousness-type double patenting over claims 1, 2, 7-9 and 14 of copending application no. 11/706,034 in view of Hellberg et al. (Journal of Medicinal Chemistry, vol. 30 (1987) pages 1126-1135). In addition, pending claims 76-81 and 101-108 were directly rejected. Specifically, claims 79-81 were rejected under 35 U.S.C. §101 as directed to non-statutory subject matter. In addition, claims 76-81 and 101-108 were rejected under 35 U.S.C. §103 as being unpatentable over a combination of Hellberg et al. in view of Voigt et al. (Journal of Cellular Biochemistry Supplement, vol. 37 (2001) pages 58-63). These rejections will be addressed below in turn.

Independent claim 76 was amended to recite receiving and using activity data characterizing a new protein variant library to develop a new sequence activity model. Similar amendments were made to independent computer readable medium claim 79. Support for these amendments is found in the pending specification at, for example, page 29, line 18 to page 31, line 4. Note that the specification discusses using feedback from the *in vitro* step to identify a new backbone for a subsequent round of *in silico* modeling. This information provides support for the aspects of amendments which recite a “new reference sequence”. Claim 79 was amended to recite "code for outputting information identifying the members of the new protein variant library." Support for this amendment is found implicitly and explicitly in Section VII, page 80, et seq. for example.

The Restriction of Claims 109-119

As indicated, various new claims were added in the previous amendment, including a new claim set, claims 109-119. At the time this claim set was added, it found support in the original and previous claims along with the disclosure found at page 30, lines 21-28. In the current Action, the Examiner subjected claims 109-119 to a restriction requirement and withdrew them from consideration. This restriction is respectfully traversed.

According to the Examiner new claims 109-119 are patentably distinct because they are drawn to a model that predicts the quantity of protein expressed while the other pending claims are drawn to a model that predicts activity. The Examiner acknowledges that both models provide

information as a function of nucleotide sequence. However, the claims are not truly drawn to types of models, rather they are both directed to methods and computer products "for identifying nucleotides for variation." Thus, method claim 109 overlaps substantially with pending method claim 76. The only significant difference between pending claim 109 and claim 76 (prior to amendment) is in that a nucleotide sequence model used in the model is related to desired activity of protein variants in claim 76 while it is related to quantity of protein expressed in claim 109. Both claims develop and use a nucleotide sequence model in the same manner. And both claims use this sequence activity model to rank positions in a reference nucleotide sequence and/or nucleotide types at specific positions in the reference nucleotide sequence. Further both claims use this ranking to identify one or more nucleotides that are to be varied or fixed.

Importantly, dependent claims 78 and 81 in the original claims recite that the activity in question is "a function of expression of nucleic acids." This feature is directly related to the "quantity of protein expressed" which is predicted by the model in claim 109.

While the claims in question are patentably distinct, they overlap so significantly that any search of one must necessarily fully consider the other to nearly the complete realm of the other. It is respectfully submitted that it would not constitute an undue burden for the Examiner to search claims 109-119 together with the remainder of the pending non-withdrawn claims. Withdrawal of the decision to restrict claims 109-119 is respectfully requested.

The Provisional Double Patenting Rejections

As mentioned, claims 76-81 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 8 of copending Application No. 11/706,034 in view of Hellberg et al. Applicants will consider this rejection again when an indication of allowable subject matter is made in either the present application or Application No. 11/706,034. Applicants note that Application No. 11/706,034 was filed after the present application.

Claim Rejections 35 USC § 101

Claims 79-81 were rejected under section 101 as being drawn to a non-statutory computer program product. Applicants understand the Examiner's position in this rejection as requiring some

type of result that is not generated outside of a computer. The Applicants do not believe that either the controlling case law or the current PTO guidelines require such transformation. This position was persuasively set forth in response to a previous rejection.

However, to expedite prosecution, Applicants have amended independent claim 79 to recite code for outputting information, in a user readable format, identifying members of the new protein variant library. Withdrawal of the rejections of these claims under section 101 is respectfully requested.

The Rejections under 35 USC § 103

All pending claims were rejected as obvious over the Hellberg et al. and Voigt et al. references. At pages 7 through 9 of the Office Action, the Examiner argues that Hellberg et al. teach aspects of operations (a) through (e) of claim 76. In items 8 and 9, the Examiner acknowledges that Hellberg et al. does not teach using a method to generate a library of protein variants as claimed. To address this deficiency in Hellberg et al., the Examiner cites Voigt et al. as teaching a mutant library and using genes to create a protein variant library.

Claim 76 as amended recites

> (d) using the ranking to identify one or more nucleotides, in the reference nucleotide sequence, that are to be varied or fixed in order to impact the desired activity;
>
> (e) generating a new protein variant library containing one or more of the protein variants in which the identified nucleotides are varied or fixed in order to impact the desired activity;
>
> (f) assaying the new protein variant library to provide activity information used to develop a new computational algorithmic sequence activity model; and
>
> (g) using the new computational algorithmic sequence activity model to identify one or more nucleotides in a new reference nucleotide sequence that are to be varied or fixed in order to impact the desired activity.

Applicants agree that Hellberg et al. fails to suggest generating a new protein variant library in vitro wherein the sequences of the members of the new protein variant library comprise the identified amino acid residues varied [or fixed] in order to impact the desired activity.

Hellberg et al. describes a general 5 step process for peptide QSAR: (1) Structural Description, (2) Design (i.e., choosing the peptides for a training set), (3) Synthesis and Biological Testing (i.e., generating the physical peptides to extract activity data for the training set), (4) Mathematical Modeling (i.e., generating the model via PLS), and (5) Postulating New Analogues (predicting which new peptide to produce). This sequence terminates at the stage of using the model to suggest new peptide analogues. It fails to reach a point where a model is used to suggest a new variant library, which is then generated.

The Examiner cites various sections of Voigt et al. as teaching generating and using a library. However, Voigt et al. describes general observations regarding available evidence as reported in the literature and elsewhere. It draws general conclusions about which residues to target in mutagenesis and recombination for directed evolution of proteins. It does not describe sequence activity model as claimed. Nor does it describe the use of these or any similar models for identifying specific residues to fix or vary in a new protein variant library. Still further, it does not suggest

> assaying the new protein variant library . . . to develop a new . . . sequence activity model.

Voigt et al. also does not propose or suggest

> using the new . . . sequence activity model to identify one or more nucleotides in a new reference nucleotide sequence that are to be varied or fixed in order to impact the desired activity.

As neither Voigt et al. nor Hellberg et al. suggest this progression of using libraries and developing models, the claimed invention is patentable over these references. Withdrawal of the rejection of claims 76-78 and 101-108 under Section 103 is respectfully requested. Withdrawal of the rejection of computer program product claims 79-81 is respectfully requested for similar reasons.

To advance prosecution, the Voigt et al. paper will now be described in more detail. The paper has three sections: an "Optimizing the Mutant Library" section, a "Targeted Mutagenesis Algorithms" section, and a "Recombination Strategies" section. None of these describes a developing a sequence activity model from training set data, particularly training set data comprising activity and a protein sequence for each protein variant in the training set. Nor does any section describe using a similar model to identify residues to vary or fix in new protein variant library.

At pages 58-60, the Voigt et al. paper contains the "Optimizing the Mutant Library" section. This section describes work in which the goal is to generally characterize the competing effects of mutation rate, library size, and mutant improvement for libraries generated using error prone PCR.

The “model” discussed in this section is characterized as a “statistical model” and presents the general plots shown in Figure 1. Nothing in the section suggests that the model is generated from a training set of information from a library. Nor does the model appear to be a sequence activity model.

In the “Targeted Mutagenesis” section, the authors employ mutagenesis data reported for directed evolution experiments to consider various individual residue positions in the sequence. For each such residue position in a subtilisin E protein, the authors employed protein design software using energetic interactions between residues to determine how many different amino acids may be substituted at a position. This represents the “site entropy” of a residue. The “Targeted Mutagenesis” section simply shows that beneficial mutations are strongly correlated with residues having a high site entropy (i.e., residues at positions where a large number of different amino acids are tolerated in the directed evolution data). This analysis is presented at the right column of page 60 and the top of the left column of page 61, including Fig. 2. This section is not relevant to generating libraries from models or developing models from library data.

A wholly separate analysis is presented in the section on “Recombination Strategies” at page 61 of the Voight et al. article. The authors describe “a computational algorithm to predict the location of crossovers, based on the assumption that the stability of the offspring need to be retained.” The algorithm counts the total number of interactions that are broken by the pattern of fragments from the parents participating in the recombination. Residues are considered interacting if their side chains are within a cut-off distance. Recombinants with minimum disruption are most likely to retain the structure of their parents and therefore have a possibility of being active.

As an example of their work in this area, the authors identified the interacting residues from the structure of the protein PurN. They then calculated the schema disruption for all possible recombination mutants from PurN and GART. The disruption is shown in Fig. 3. Many of the mutants having the least disruption were the ones found experimentally to be functional.

No other algorithms or examples are presented in the *Recombination Strategies* section of the paper. This section simply describes an algorithm used to identify the number of interacting residues in a recombinant protein. It does this by considering the spatial arrangement of side chains in a computational representation of a recombinant protein having a particular crossover position. It measures the distance between residues and counts the number of side chain interactions that are broken.

The described algorithm is not developed from a training set of information from a library. It is an *a priori* approach to that does not make use of sequence-activity data from a training set. Further, it does not constitute a "sequence activity model that predicts activity as a function of amino acid residue type and corresponding position in the sequence" as recited in the independent claims. Still further, it does not suggest using a sequence activity model to identify residues to vary or fix in new protein variant library.

Because the methodology and algorithms described in the Hellberg et al. and Voight et al. paper fail to suggest, collectively, using a model to identify residues to vary or fix in new protein variant library, or using the new library in developing a new sequence activity model they do not render the independent claims (claims 76, 79 and 109) unpatentable. Withdrawal of the art rejections of all claims is respectfully requested.

As previously mentioned, new claims 109-119 recite methods and computer program products for identifying nucleotides for variation in a nucleotide sequence in order to optimize the expression properties of the nucleotide sequence. Specifically, the variations in the nucleotide sequence are for impacting "the quantity of protein expressed." Some other features from the previously pending claims are recited in these claims. For at least the reasons set forth above, it is respectfully submitted that new claims 109-119 are patentable over the cited art.

Claims 78 and 81 recite that the activity in a sequence activity model "is a function of expression of nucleic acids." There is no basis for concluding that these claims are unpatentable over the cited art and non-has been presented in the prosecution to date. It is respectfully submitted that claims 78 and 81 are patentable over the cited art.

Conclusion

Applicants believe that all pending claims are allowable and respectfully request a Notice of Allowance for this application from the Examiner. Should the Examiner believe that a telephone conference would expedite the prosecution of this application the undersigned can be reached at the telephone number set out below.

If any fees are due in connection with the filing this Response, the Commissioner is hereby authorized to charge such fees to Deposit Account 504480 (Order No. MXGNP004X1).

Respectfully submitted,

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